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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,054	11/20/2003	Stephen N. Jones	07917-178001 / UMMC 03-14	3347

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EXAMINER	
SGAGIAS, MAGDALENE K	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 02/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/719,054	JONES ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1- 32* is/are pending in the application.

4a) Of the above claim(s) *1-22,30 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-29 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/21/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-32 are pending.

Applicant's election with traverse of the invention of group XIII claims 23-29 and 32 in the reply filed on December 13, 2005 is acknowledged. The traversal is on the ground(s) that claim 23 is a linking claim that this links groups XIII and XIV therefore should be treated as such. This is not found persuasive because restriction requirements are set forth for reasons of patentability distinction between each independent invention so as to warrant separate search burden as well as examination. The examiner maintains that groups XIII and XIV are patentably distinct because each of the groups is directed to patentably distinct methods that require distinct method steps and products having different functions. For example, group XIII is directed to a method of treating a subject that has a Wnt5a associated hematopoietic cancer which has distinct and different method steps of making, distinct structure and utilities compared to method steps of treating a subject who is at risk of developing said cancer of group XIV.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-22 and 30-31 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction requirement in the reply filed on December 13, 2005.

Claims 23-29 and 32 are under consideration.

Claim Objections

1. Claim 23-29 and 32 are objected to because of the following informalities:

Claim 23-29 and 32 are objected to because they read on a non-elected invention.

Claim 23 is objected to because the gene Wnt5a should be spelled out, in full, in the first occurrence of the term. Appropriate correction is required.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23-29 and 32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claimed invention encompasses a method of treating a subject who has a Wnt5a associated hematopoietic cancer by administering to the subject a nucleic acid molecule comprising a sequence that encodes a Wnt5a biologically active fragment or mutant thereof, protein wherein the expression of Wnt5a biologically active fragment or mutatnt thereof protein results in a therapeutically effective amount of Wnt5a biologically active fragment or mutant thereof.

When the claims are analyzed in light of the specification, instant invention encompasses a polynucleotide sequence corresponding to a Wnt5a biologically active fragment or mutant thereof. The claimed genus encompasses any polynucleotide sequence corresponding to a Wnt5a biologically active fragment or mutant thereof. In analyzing whether the written description requirement is met for the genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the specification fails to disclose any Wnt5a biologically active fragment or mutant thereof polynucleotide sequence. The specification does not provide any disclosure as to what would have been the sequence structure of a representative number of species of the claimed broad genus which encompasses any Wnt5a biologically active fragment or mutant thereof polynucleotide sequence that will generate a therapeutically effective amount of Wnt5a biologically active fragment or mutant thereof in a cell. In the instant case, the specification discloses the use of wild type Wnt5a which has been isolated from human or mouse, however, there is no description as to what would have been the complete structure for the sequence of Wnt5a biologically active fragment or mutant thereof isolated from any mammalian or non-mammalian species and how it is related

Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics, specific features and functional attributes that would distinguish Wnt5a biologically active fragment or mutant thereof different members of the claimed genus. In the instant case, the only characteristics described is function that the fragment/mutant will treat a subject who has Wnt5a-associated hematopoietic cancer but since all the species will have all that characteristic such cannot be used to distinguish one from the other. Applicant's specification does not teach what are the

characteristics of polynucleotide sequences from any mammalian and non-mammalian species except for the wild type human or mouse Wnt5a.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that applicant is in possession of the genus of wnt5a nucleic acid molecules, including fragments and mutants thereof other than human and mouse at the time of application was filed. Thus, it is concluded that the written description requirement is not satisfied for the claimed genus.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23-29 and 32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method of treating a subject having, a Wnt5a-asociated hematopoietic cancer by administering to the subject a cell comprising a nucleic acid molecule that encodes Wnt5a protein or a biologically active fragment or mutant thereof, wherein the amount of the nucleic acid sequence molecule delivered is sufficient to generate therapeutically effective amount of Wnt5a. Dependent claims limit the subject to a human patient with acute myeloid leukemia. Dependent claim 32 further limit the invention wherein a subject is treated for said cancer by administering a cell removed from the subject, transducing the cell with a nucleic

acid molecule encoding Wnt5a protein or a biologically active fragment or mutant thereof, and optionally a sequence that encodes a detectable marker, optionally culturing the cell and returning the cell to the subject.

In determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are; the breadth of the claims, the nature of the invention, the state of the art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

These factors are analyzed, in turn, and demonstrate that one of ordinary skill in the art will need to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art

at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The claims are directed to a method of treating a subject having, a Wnt5a-asociated hematopoietic cancer by administering to the subject a cell comprising a nucleic acid molecule that encodes Wnt5a protein or a biologically active fragment or mutant thereof, wherein the amount of the nucleic acid sequence molecule delivered is sufficient to generate therapeutically effective amount of Wnt5a. Dependent claims limit the subject to a human patient with acute myeloid leukemia. Dependent claim 32 limit the invention wherein a subject is treated for said cancer by administering a cell removed from the subject, transducing the cell with a nucleic acid molecule encoding Wnt5a protein or a biologically active fragment or mutant thereof, and optionally a sequence that encodes a detectable marker, optionally culturing the cell and returning the cell to the subject.

The specification discusses that Wnt5a plays a role in B cell proliferation and differentiation, and acts as tumor suppressor of B cell proliferation to suppress hematopoietic malignancies (specification p 2, lines 23-24). The specification describes that hematopoietic cancers are associated with a reduction in Wnt5a gene expression or protein activity including acute myeloid leukemia (AML) (specification p 4, lines 26-30). The specification recites that "The new methods and compositions described herein are based, in part, on studies that have established Wnt5a as a tumor suppressor in B cells of two mammalian species and the present experiments were conducted in mice and humans and there is no reason to expect that the findings are not applicable to all Wnt5a-expressing cells and animals" (specification p 13 lines 10-25). The specification further contemplates that cells can be obtained from the subject, transduced with Wnt5a or mutants thereof, in vitro, and then the cells per se can be administered to subjects in the context of replacement therapies. Wnt5a gene is linked to a

native Wnt5a promoter and/or other regulatory sequences and introduced into a cell, for example, a B cell that has reduced level of Wnt5a that was previously removed from the subject. The cell can be expanded in culture for some time, and when the cell is returned to the subject, the cell expresses normal amount of Wnt5a. The specification contemplates that such methods can be used to treat a disease associated with reduced Wnt5a expression such as a hematopoietic malignancy (specification p 36-37). The Wnt5a nucleic acid molecules inserted into vectors can be used as gene therapy vectors delivered to a subject by intravenous injection or local administration or by stereotactic injection (specification p 41). While the specification provides extensive teachings pertaining to Wnt5a protein expression, in vitro or in vivo (specification p 32-37), the specification fails to provide any relevant teachings or specific guidance or working examples with regard to transducing a cell ex vivo with wnt5a and/or obtaining any cells from a subject, transduce cells ex vivo with wnt5a or a biologically active fragment or mutant thereof, reintroduce the cells into the subject wherein therapeutic levels of the transgene are produced to treat a subject with Wnt5a hematopoietic cancer, particularly AML. Thus, as enablement requires the specification to teach how to make and use the claimed invention, the specification fails to enable the claimed methods for treating cell based Wnt5a associated hematopoietic cancer and particularly AML. It would have required undue experimentation to make and use the claimed invention without a reasonable expectation of success.

The claims are directed to methods of treating Wnt5a associated hamatopoietic cancer, particularly AML in a subject by transdcucing a cell with Wnt5a ex vivo, producing a therapeutic protein in a cell or hematopoietic tissue and clearly fall into the realm of gene therapy. The specification has contemplated treating Wnt5a associated AML by cell based Wnt5a gene therapy, such that treatment can be achieved by transplantation of the transduced cells to a

target tissue in sufficient number to produce therapeutic levels of the Wnt5a protein or biologically active fragment or mutant thereof, but has not provided any specific guidance or working examples that correlate to treatment of any Wnt5a associated hematopoietic cancer, particularly AML by the claimed methods. Since the instant specification has failed to provide specific guidance or working examples correlating to treatment of any Wnt5a hematopoietic cancer particularly AML by claimed method one of skill in the art could not rely on the state of the cell based gene therapy art to treat AML by way of the claimed methods. This is because the art of cell based gene therapy is an unpredictable art with respect to multiplying transduced cells in vitro, source of the cell for therapy, immunological issues, levels of expression of a therapeutic protein necessary to provide therapy, the number of transduced cell needed and mode of administration of the therapeutic cell. These issues are discussed by experts in the field of gene therapy, in published reviews at the time of the instant invention. Cage, (Nature, 392: 18-24, 1998) teach that although the hematopoietic field is the most advanced in clinical applications of cell therapy, the number of cells needed to perform the desired function is a limiting variable, and thus the ability to multiply a population of cells may be critical (p 20, 2nd column). The author further noted that difficulties arise as if the cells either cannot self-renew in vitro, as in the heamatopoietic system (p 20, 2nd column). Cage, also describes that although, the use of allogeneic obviates the time and source restrictions inherent in the use of autologous cells, many of the problems associated with the variability and replicative capacity remain (p 21 1st column). In addition, when considering the functional requirements of a cell and the limitations imposed by the source of the cell, it becomes clear that there is no single universal donor cell that will be useful for all diseases (Cage, p 23 1st column).

The specification, failed to guidance and/or working examples with respect to cell targeting, route of administration of transduced cells, dose of transduced cells and levels of

gene expression in vivo necessary to treat a subject with a Wnt5a associated hematopoietic cancer. The specification has contemplated the use of cell-based therapy methods of gene transfer for introducing Wnt5a or a biologically active fragment or mutant thereof therapeutic gene, into a hamatopoietic cell such as a B cell or hematopoietic stem cell and reintroducing the cell into the subject (specification p 41-42). The specification however, has not provided any specific guidance or teachings with regard to recombinant cell based methods of Wnt5a or a biologically active fragment or mutant thereof, gene therapy and as to what doses and modes of administering a recombinant therapeutic cell population encompassed by the claims. Kohn et al, (J Intern Med, 249(4): 379-90, 2001) noted that inefficient gene transfer to human hemotopoietic stem cells has imposed the major limitation to successful application of gene therapy (p 379, abstract). While progress has been made in recent years for gene transfer in vivo, AML cell based therapy in vivo continues to be unpredictable and inefficient as supported by numerous teachings available in the art.

In light of the above, it appears that the state of the art is suggesting that Wnt5a cell based gene therapy in AML subjects currently remains unpredictable and undeveloped. The instant specification does not provide any relevant teachings, specific guidance, or working examples for overcoming the limitations of Wnt5a cell based gene therapy raised by the state of the art. Therefore, the skilled artisan would conclude that the state of the Wnt5a cell based gene therapy is undeveloped and unpredictable at best. Given the lack of guidance provided by the instant specification, it would have required undue experimentation to practice the invention as claimed for treating AML by Wnt5a cell based gene therapy without a reasonable expectation of success.

With regard to use of the claimed methods fro treating wnt5a associated hematopoietic cancer, particularly AML, it would appear that the issues regarding a cell based gene transfer

system to the Wnt5a hematopoietic associated cancer cells or tissues, as discussed above with respect to Wnt5a gene therapy, are also relevant when considering the contemplations of the instant specification. The specification fails to provide teachings, specific guidance, or working examples that correlate to the treatment of Wnt5a associated hematopoietic cancer, particularly AML, by way of the claimed methods. Furthermore, the instant specification fails to provide the skilled artisan with guidance for targeting Wnt5a associated hematopoietic cancer cells or tissues with a cell comprising a Wnt5a therapeutic gene the expression of which could result in treatment of Wnt5a associated hematopoietic cancer particularly AML after cell transplantation into a subject. In addition, the specification does not provide specific guidance regarding the number of transduced Wnt5a or biologically active fragment or mutant thereof, level of expression of the therapeutic Wnt5a gene necessary for treating Wnt5a associated hemotopoietic cancer and AML. Moreover, the state of the art of Wnt5a cell based hematopoietic gene therapy is unpredictable and undeveloped. The state of the art lack relevant teachings as to what would be the therapeutic Wnt5a recombinant levels produced in the target hematopoietic cancer cells to treat a subject with Wnt5a associated hematopoietic cancer. In addition, neither the specification nor the art of record provide any guidance for removing a cell from a subject of any hemtopoietic cell type transducer the cell with Wnt5a gene, or a biologically active fragment or mutant thereof, culturing the cell and returning the cell into the subject and as to what would be the appropriate cell dose and route of administration to treat Wnt5a associated hematopoietic cancer. It is noted that the claimed invention is a mere proposal of the idea of using Wnt5a cell based gene therapy for treatment of Wnt5a associated cancer and AML in a subject and in humans. The specification does not teach what deletion(s), substitution(s), insertion(s), addition(s) and/or replacement(s) of nucleotide sequences, for example by means of mutagenesis of the DNA is needed for practicing the claimed method.

The specification does not provide any guidance and/or working examples as to what type of cells are needed to be obtained from the subject to be transduced with mutant nucleic acid molecules before reintroduce the transduced cells into the subject. Therefore, the skilled artisan would conclude the state of the art of Wnt5a and a biologically active fragment or mutant thereof of Wnt5a gene therapy is undeveloped and unpredictable at best. Given the lack of guidance provided by the instant specification, it would have required undue experimentation to practice the invention as claimed for treating Wnt5a associated hematopoietic cancer by Wnt5a cell based gene therapy without a reasonable expectation of success.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the treatment of a Wnt5a associated hematopoietic cancer, particularly AML, the lack of guidance provided by the specification for the treatment of Wnt5a associated hematopoietic cancer, the absence of working examples that correlate to the treatment Wnt5a associated hematopoietic cancer, particularly AML, the unpredictable state of the art with respect to cell based gene therapy, the undeveloped state of the art pertaining to the treatment of Wnt5a associated hematopoietic cancer, and particularly AML by Wnt5a cell based gene therapy, and the breadth of the claims directed to Wnt5a, or a biologically active fragment or mutant thereof, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 26 is vague and indefinite because it recites the phrase "in connection with a liposome". It is not clear as to what the term "connection" means in relation to the liposome.

Conclusion

4. **No claim is allowed**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram R. Shukla, can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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